Remarks

Claims 1-31 were pending in the subject application. By this Amendment, claims 12, 17-19, and 25 have been amended, claims 1-11, 23, and 27-31 have been cancelled, and new claims 32-43 have been added. The undersigned avers that no new matter is introduced by this Amendment. Support for the new claims and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 12-22, 24-26, and 32-43 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, claims 12, 17-19, and 25 have been amended and claims 32-43 have been added. Support for the amendment to claim 12 can found, for example, at page 13, lines 31-32; page 14, lines 1-29; page 31, lines 1-3 and 14-17; page 33, lines 15-23; page 47, lines 1-3; and page 52, lines 17-32 of the specification as filed. Support for claim 17 can be found, for example, at page 31, lines 1-3 and 14-17 of the specification as filed. Claims 18 and 19 have been amended for antecedent basis. Support for the amendment to claim 25 can be found, for example, at page 38, lines 8-10 of the specification as filed.

Support for new claims 32 and 33 can be found, for example, at page 14, lines 13-29, and page 33, lines 15-23 of the specification as filed. Support for claim 35 can be found, for example, at page 47, lines 14-17; page 48, lines 11-19; and page 52, lines 15-32, of the specification as filed. Support for new claims 36, 38, and 39 can be found, for example, at page 13, lines 31-32; page 14, lines 1-29; page 31, lines 1-3 and 14-17; page 33, lines 15-23; page 47, lines 1-3; and page 52, lines 17-32 of the specification as filed. Support for claims 34 and 37 can be found, for example, at page 6, lines 25-28, and page 7, lines 8-21 of the specification as filed. Support for new claims 40-43 can be found, for example, at page 47, lines 1-32; page 48, lines 1-19; and page 52, lines 15-32 of the specification as filed.

Claim 25 is rejected under 35 USC §112, second paragraph, as indefinite. The Office Action indicates that claim 25 is indefinite because it indicates that surfactant protein B is a regulatory sequence that can be operably linked to a polynucleotide, and that surfactant protein B is a polypeptide, not a regulatory sequence that can be operably linked to a polynucleotide. By this

Amendment, Applicants have amended claim 25 to clarify that the regulatory sequence is a surfactant protein B promoter, a steroid response element, or both. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 12, 13, 16-18, 22, and 26 are rejected under 35 USC §102(b) as anticipated by Leaman *et al.* (*Virology*, 2002, 292:70-77). The Examiner indicates that the Leaman *et al.* publication teaches a method of treating RSV infection in African green monkeys by intranasal administration of an antisense oligonucleotide directed against RSV RNA. By this Amendment, Applicants have amended independent claim 12 to recite that the method comprises administering a nanoparticle to airway cells in the subject, wherein the nanoparticle comprises a polynucleotide conjugated to chitosan, and wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631; 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. As the Leaman *et al.* publication describes an experiment in which an antisense oligonucleotide is administered to African green monkeys, the Leaman *et al.* publication does not anticipate the claimed method as currently amended. New claims 36-43 are also not anticipated at least for this reason. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 12, 13, 15, 17-19, 22 and 26 are rejected under 35 USC §102(b) as anticipated by Torrence *et al.* (U.S. Patent 5,998,602). The Office Action indicates that Torrence *et al.* teach methods of treating RSV infection in humans by inhalation of an aerosol comprising an antisense oligonucleotide directed against RSV RNA. As indicated above, by this Amendment, Applicants have amended independent claim 12 to recite that the method comprises administering a nanoparticle to airway cells in the subject, wherein the nanoparticle comprises a polynucleotide conjugated to chitosan, and wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA). As the Torrence *et al.* patent proposes administering an antisense oligonucleotide to treat RSV infection, the Torrence *et al.* patent does not anticipate the claimed method as currently amended. New claims 36-43 are also not anticipated at least for this reason.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 12, 13, 15-18, 22-24, and 26 are rejected under 35 USC §102(b) as anticipated by McSwiggen *et al.* (U.S. Patent 5,693,532). The Office Action indicates that the McSwiggen *et al.* patent teaches methods of inhibiting replication of RSV *in vivo* through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. By this Amendment, Applicants have amended independent claim 12 to recite that the method comprises administering a nanoparticle to airway cells in the subject, wherein the nanoparticle comprises a polynucleotide conjugated to chitosan, and wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA). As the McSwiggen *et al.* patent proposes administering a ribozyme to inhibit RSV replication, the McSwiggen *et al.* patent does not anticipate the claimed method as currently amended. New claims 36-43 are also not anticipated at least for this reason. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 12, 13, 15, 20, 22-24, and 26 are rejected under 35 USC §102(b) as anticipated by Barik (U.S. Patent 5,831,069). The Examiner indicates that the Barik patent teaches methods of killing RSV virus in an individual in need of such treatment by contacting the virus with an effective dose of an antisense oligonucleotide. By this Amendment, Applicants have amended independent claim 12 to recite that the method comprises administering a nanoparticle to the subject, wherein the nanoparticle comprises a polynucleotide conjugated to chitosan, and wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA). As the Barik *et al.* patent proposes administering an antisense oligonucleotide to kill RSV in the subject, the Barik *et al.* patent does not anticipate the claimed method as currently amended. New claims 36-43 are also not anticipated at least for this reason. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 12-19, 22-24, and 26 are rejected under 35 USC §103(a) as obvious over McSwiggen *et al.* (U.S. Patent 5,693,532). The Office Action indicates that McSwiggen *et al.* teach methods of inhibiting the replication of RSV *in vivo* through use of ribozymes targeted to RSV mRNA for treatment of diseases, and asserts that it would have been obvious to one of ordinary skill in the art at

the time of the invention to administer the ribozymes of McSwiggen *et al.* to a subject not suffering from RSV infection to prevent RSV infection or to serve as an experimental control. Applicants respectfully assert that the claimed invention is not obvious over the cited reference and traverse the rejection of record.

As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention (*CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) citing *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974)). McSwiggen *et al.* fail to teach or suggest many of the limitations recited in the presently pending claims. For example, the reference discloses administration of ribozymes and fails to teach or suggest a nanoparticle comprising a polynucleotide conjugated to chitosan, wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA), as recited in claim 12 as currently amended. New claims 36-43 are also not obvious at least for these reasons. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

Claim 21 is rejected under 35 USC §103(a) as obvious over McSwiggen *et al.* (U.S. Patent 5,693,532) as applied to claims 12-19, 22-24, and 26 above, and further in view of Tuschl *et al.* (U.S. Patent Application 2004/0259247) and Leaman *et al.* (*Virology*, 2002, 292:70-77). The Office Action indicates that it would have been obvious to one of ordinary skill in the art at the time of the invention to make and use siRNAs capable of inhibiting the expression of RSV mRNA in a subject in view of the combined teachings of Tuschl *et al.* (siRNA), Leaman *et al.* (inhibition of RSV with antisense oligonucleotides), and McSwiggen *et al.* (inhibition of RSV mRNA encoding NS1 or NS 2 with ribozymes). Furthermore, the Office Action indicates that one of ordinary skill in the art would have been motivated to substitute siRNAs for the ribozymes disclosed by McSwiggen *et al.* with a reasonable expectation of success, because Tuschl *et al.* taught that siRNAs are in general significantly more potent than ribozymes. Applicants respectfully assert that the claimed invention is not obvious over the cited reference and traverse the rejection of record.

As indicated above, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention. The cited references fail to teach or suggest all of the limitations recited in the presently pending claims. For example, none of

the cited references teach or suggest administration of a nanoparticle comprising a polynucleotide conjugated to chitosan, wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA), as recited in claim 12 as currently amended.

Furthermore, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP §2143.01. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); MPEP §2143.02. The primary reference, the McSwiggen *et al.* patent, teaches methods of inhibiting replication of RSV *in vivo* through use of specific ribozymes targeted to RSV mRNA for treatment of diseases in man and other animals. However, the McSwiggen contains no empirical data, *in vitro* or *in vivo*, demonstrating that the ribozymes can be effectively delivered to respiratory cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. With respect to the Tuschl *et al.* publication, the Office Action indicates that this reference "taught and/or suggested both *in vitro* transfection and *in vivo* delivery of siRNAs for therapeutic purposes." Example 2 of Tuschl *et al.* demonstrates gene silencing in mammalian cells *in vitro*; however, there is no empirical evidence in the cited references that the siRNAs can be effectively delivered to airway cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. These references would not predictably generate success in delivering a nanoparticle comprising a polynucleotide conjugated to chitosan to airway cells, wherein the polynucleotide is an siRNA or expresses an shRNA, such that expression of an RSV gene or transcript is reduced. Those of ordinary skill in the art would recognize that *in vitro* assays and/or cell culture-based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, the cited references do not establish a clinical correlation. The greatly increased complexity of the *in vivo* environment compared to the controlled conditions of an *in vitro* assay does not permit extrapolation to human clinical efficacy with any reasonable degree of predictability. It is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their

propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the endogenous systems involved in homeostatic regulation *in vivo*. Cellular metabolism may be more constant *in vitro*, but may not truly be representative of the tissue from which the cells were derived.

The Leaman *et al.* publication teaches coupling tetrameric 2'-5'-linked oligoadenylates (2-5A) to an antisense oligonucleotide complementary to repetitive gene-start sequences within the RSV genome. 2'-O-methyl antisense moieties were used to confer enhanced stability *in vivo* and higher affinity for target sequences. The results achieved using this single chimeric antisense construct cannot be predictably extrapolated to results with a nanoparticle comprising a polynucleotide conjugated to chitosan, wherein the polynucleotide is an siRNA or expresses an shRNA. New claims 36-43 are also not obvious at least for these reasons. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

Claim 25 is rejected under 35 USC §103(a) as obvious over McSwiggen *et al.* (U.S. Patent 5,693,532) as applied to claims 12-19, 22-24, and 26 above, and further in view of Prince *et al.* (U.S. Patent 5,290,540) and Huang *et al.* (U.S. Patent 6,586,579). The Office Action indicates that it would have been obvious to one of ordinary skill in the art at the time of the invention to use a steroid inducible element to modulate expression of the ribozyme taught by McSwiggen *et al.*, as modified by Prince *et al.*, because the combined methods call for the use of steroids in the lung, and one of ordinary skill would perceive that a steroid response element would allow the controllable induction of anti-viral ribozyme expression.

As indicated above, all the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention. McSwiggen *et al.* fail to teach or suggest many of the limitations recited in the claims as currently amended. For example, the reference discloses administration of ribozymes and fails to teach or suggest a nanoparticle comprising a polynucleotide conjugated to chitosan, wherein the polynucleotide is a small interfering RNA (siRNA) or expresses a small hairpin RNA (shRNA), as recited in claim 12 as currently amended. New claims 36-43 are also not obvious at least for these reasons. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

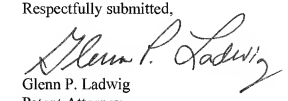
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Glenn P. Ladwig
Patent Attorney
Registration No. 46,853
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

GPL/jnw